Cycloadditions in aqueous media

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Chapter 4

On the Origin of the 'Aqueous Acceleration' of Cycloadditions : Excluding Hydrophobic Interactions. Retro Diels-Alder Reactions[1]

Kinetic studies of a specific homo and hetero retro Diels-Alder reaction in aqueous media are presented and discussed in this chapter. The former reaction monitors the ability of water to promote cycloadditions only through hydrogen-bond interactions and this study also reflects how bimolecular Diels-Alder reactions are affected by hydrogen bonding of water. In the latter case an equilibrium is established and the effect of aqueous media on the equilibrium constant is discussed. Combined with results discussed in the previous chapters a complete picture of Diels-Alder reactions in water, aqueous mixtures and micellar solutions can be designed.

4.1. Introduction

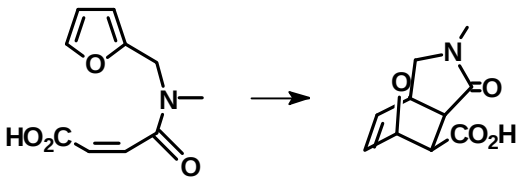
The discovery of the acceleration of Diels-Alder (DA) reactions in water was first met with curiosity, but by now a large number of DA reactions have been carried out in water and kinetic, thermodynamic and theoretical investigations have shown that both hydrogen-bond interactions and enforced hydrophobic interactions are responsible for the rate enhancements[2] (see previous chapters). In Chapter 3 the problem of separating the different contributions to the promotion of DA reactions by water was discussed. However, since most DA reactants are both hydrophobic and susceptible to hydrogen-bond interactions, it is not easy to study this matter experimentally. For this reason mainly computational studies have been used to shed some light on this matter[3,4].

In Chapter 3 a DA reaction was described in which the influence of hydrogen-bond interactions could be neglected. Consequently, this system provided the opportunity for studying how water promotes a cycloaddition purely through hydrophobic interactions. Water-induced acceleration of this particular reaction is moderate, although the limited hydrophobicity of the reactants has to be taken into account.

In this chapter the complementary reaction is presented. The kinetics of the homo retro Diels-Alder (RDA) reaction of a substituted anthracenedione furnishes an estimate of the contribution of hydrogen-bond interactions to the promotion of cycloadditions by water. Due to the unimolecular nature of this transformation and its negligible volume of activation ($\Delta^{\neq}V^{\theta}$) this reaction serves as an excellent probe for examining the influence of water on this type of reactions, in the absence of enforced hydrophobic interactions. Essential is the fact that no significant reduction of the solvent-accessible surface-area takes place during the activation process.

The hetero RDA reaction of a dihydro oxazine was studied. The substituents on which water can exert its polarising effect are part of the six-membered ring that is broken in the reaction. Therefore, a distinctly different behaviour of this probe in water was anticipated.

The analogy with rate enhancements of the Claisen rearrangement in aqueous media was mentioned in the previous chapters. A second important unimolecular pericyclic reaction is the intramolecular Diels-Alder (IMDA) reaction, shown in Scheme 4.1[5]. These IMDA reactions have been carried out in aqueous solutions and were also found to be promoted by this solvent[5,6]. The reaction in Scheme 4.1 proceeds more than a thousand times faster in water compared to dichloromethane. Comparison with the kinetics of IMDA reactions in 2,2,2-trifluoroethanol (TFE) strongly suggests that enforced hydrophobic interactions contribute significantly to the ease of the cyclisation in water.



4.1 **4.2**

Scheme 4.1

4.2 Retro Diels-Alder Reactions : Mechanism, Solvent Effect and Applications

DA reactions are reversible processes and the reverse of the bimolecular (forward) DA reaction (which will be referred to in this chapter as BDA reactions) is known as the retro DA reaction (RDA reaction)[7]. Both organic transformations share many mechanistic features. The principal similarity is the identical activated complex (AC) which is a consequence of the principle of microscopic reversibility[8]. The initial states of both reactions are different, but resemble each other and for both reactions polarisation of the bonds during the activation process leads to the same AC. Related to this feature are the similar substituent effects on the RDA reaction : electron-withdrawing substituents on the (future) dienophile or

electron-releasing substituents on the (future) diene promote the reaction[9]. Furthermore, for both BDA and RDA reactions Lewis acids[10] and polarising solvents[11] facilitate these transformations. A curious feature of the RDA reaction is its small volume of activation[12], close to 0 $cm^3\ mol^{-1}$, in contrast to $\Delta^{\neq}V^{\theta}$ of -30 to -50 $cm^3\ mol^{-1}$ for BDA reactions[13]. This pattern points to a highly ordered AC which, in a geometrical way, resembles the cycloadduct. A logical consequence of the geometrical kinship of reactant and AC for the RDA reaction is the very small entropy of activation ($\Delta^{\neq}S^{\theta}$), generally within the range of $\pm$ 10 $J\ K^{-1}\ mol^{-1}$. Consequently, the enthalpy of activation ($\Delta^{\neq}H^{\theta}$) governs the Gibbs energy of activation ($\Delta^{\neq}G^{\theta}$)[9-12].

A femtosecond-resolved mass spectroscopic study on two simple RDA reactions, lead the authors to propose that DA reactions do not proceed via a single pathway, but via simultaneously present pathways[14]. This recent paper introduces a most interesting way of looking at DA reactions.

The RDA reaction is by no means a mechanistic oddity, but has convincingly proven its synthetic value[15]. It was first used as a synthetic tool by Diels in 1938[16]. In combination with the BDA reaction the RDA reaction is frequently encountered in the synthesis of natural products, where it serves as the last transformation in a most useful protection-deprotection sequence[17]. This sequence is particularly attractive, because, as for its bimolecular counterpart, the RDA reaction allows the stereospecific formation (or regeneration) of an unsaturated bond.

The valuable aspect of the RDA reaction is the fact that it is generally a thermally induced process, no reagents (for example acid, base) that could interfere with other parts of the reactant are involved. However, this is also its greatest drawback, since high reaction temperatures may induce racemisation of the newly formed stereocentres, thus cancelling the advantages of the cycloreversion. This limitation has been largely overcome by the use of flash vacuum thermolysis (FVT) and using this technique the RDA reaction has been widely implemented[7].

Important areas where the RDA reaction has emerged as a powerful tool are the syntheses of cyclopentenones, cyclohexenones (including quinones), furans and unsaturated γ-lactones[18], which are usually limited by the sensitivity of the products towards acidic or basic media. The RDA reaction has been further applied in the synthesis of terpenic compounds, pheromones and many other natural compounds[19]. Another useful application of the RDA reaction involves the generation of reactive molecules, for example allenes, ketenes, ketenimines, enols, enamines or molecules containing small rings[20]. Here FVT is also extensively employed, since this technique permits facile trapping of the reactive species. Usually the desired compound is the dienophilic part of the RDA reaction, whereas anthracene, cyclopentadiene or other (pseudo-)aromatic species serve as the future diene. The re-aromatisation, which provides enhanced stability of the latter compounds, is the driving force for the cycloreversion. Finally, a number of BDA reactions are accompanied by a fast RDA reaction. For example, the addition of dienophiles to aromatic azadienes (oxazoles, diazines, triazines, tetrazines, see

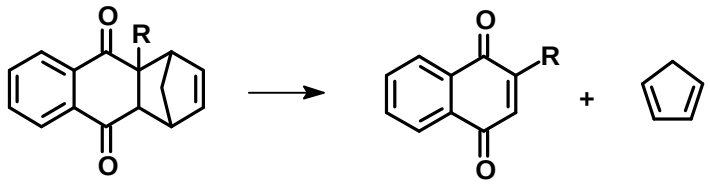
Chapter 2) are generally followed by a rapid RDA reaction with loss of nitrogen or nitriles. The facile latter step is favoured by the relief of strain and the stability of the products of the RDA reaction.

In addition to FVT, various methods of facilitating the RDA reactions have appeared in the literature. Similar to the BDA reaction, Lewis acids catalyse the RDA reaction[10]. Also examples of specific-acid catalysis[21], antibody catalysis[22], silica gel[23] and alumina catalysis[24] have been reported. Grieco demonstrated that N-alkyl-2-azanorbornenes readily cyclorevert in aqueous media, whereas rigorous conditions are required in organic solvents[25,26]. In the latter study $CuSO_4$ is added to the aqueous solution. However, the exact role of $CuSO_4$ remains unclear.

No detailed kinetic investigations of RDA reactions in aqueous media have been published. But some information is provided by computational studies in which cycloadditions along the entire reaction pathway in water have been simulated. The final part (going from the transition state to the product) is in effect the pathway for the RDA reaction and therefore these data can be compared to our experimental results. For the DA reaction of cyclopentadiene with methyl vinyl ketone, Jorgensen[3a] computed a $\Delta\Delta^{\neq}G^{\theta}$ of 13 kJ mol^{-1}, whereas Furlani and Gao[4] obtained 2.5 kJ mol^{-1}. Later, Jorgensen somewhat modified the result of his initial calculation[3b], but a discrepancy clearly remains. However, taking into account the presence of two carbonyl substituents in **4.3a**, a reduction of the $\Delta^{\neq}G^{\theta}$ by 12-16 kJ mol^{-1} is anticipated.

4.3 Homo Retro Diels-Alder Reaction : Results and Discussion

In this section rate constants of the RDA reaction of anthracenedione **4.3a** (Scheme 4.2) in different media are presented and discussed. This particular cycloreversion was previously examined by Desimoni and co-workers[11]. As part of a series of DA reactions, the rates of the RDA reaction of **4.3a** were shown to correlate with the acceptor number (AN) of the solvent. The acceptor number of a solvent is an indicator of its electrophilicity, a property closely related to its hydrogen-bond donating ability. Interaction with the solvent alters the energy of the molecular orbitals (MO) of the reactant, thus



4.3a : R = Me
b : R = H

4.4a : R = Me
b : R = H

4.5

Scheme 4.2

affecting the reaction rate. Desimoni[11] further showed that the Gibbs energies of activation for the RDA and the BDA reaction are linearly related for a wide range of solvents, as both reactions have nearly the same AC.

It is reasonable that this correlation will also be found for water, with the only exception that enforced hydrophobic interactions provide an additional contribution to the reactivity of the BDA reaction and not to that of the RDA reaction. Hence, we can separate and quantify the two factors that are responsible for rate enhancements of the BDA reaction in water.

4.3.1 Homo Retro Diels-Alder Reaction in Aqueous Solutions and in Organic Solvents

In Table 4.1 rate constants for the RDA reaction are compiled including a number of rate constants which were calculated from previously reported activation parameters[11]. The fluorinated alcohols were chosen as solvents of interest in view of their strong hydrogen-bond donating capacity.

The RDA reaction (Scheme 4.2) is exceptionally fast in water compared to organic solvents, the reaction rate only being faster in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). Compared to the apolar and aprotic solvent hexane the reaction proceeds nearly 140 times faster in water. This important result unambiguously shows how water promotes a pericyclic reaction, only by exerting its polarising influence on the substrate through hydrogen bonding. The efficiency of this hydrogen-bond interaction may be partly ascribed to the small size of water molecules, which permits the formation of 2-3 hydrogen-bonds to a carbonyl group[3]. Likewise, hydrogen bonding of water is, to a certain extent, responsible for the reduction of $\Delta^{\neq}G^{\theta}$ for BDA reactions in aqueous media. Figure 4.1 depicts a good correlation of the $\Delta^{\neq}G^{\theta}$ for the cycloreversion and the $E_T(30)$ value of the solvent. The latter parameter is an accepted indicator of the polarity and hydrogen-bond donating capacity of solvents[27]. Therefore, this observation supports the importance of these solvent properties in determining the reactivity of **4.3a**

Table 4.1 *First-order Rate Constant for the RDA Reaction of* ***4.3a*** *at 40.0 °C in Organic Solvents and Water.*

	Solvent	k_1 / 10^{-8} s^{-1}	$\Delta^{\neq}G^{\theta}$ / kJ mol^{-1}	E_T (30)	AN
1	n-Hexane[a]	2.6	122.3	31.0	0
2	Benzene[a]	6.6	119.9	34.3	8.2
3	DMSO[a]	23	116.6	45.1	20.4
4	2-PrOH[a]	27	116.2	48.4	33.6
5	Acetic acid[a]	62	114.0	51.7	52.9
6	TFE	161	111.5	59.8	53.3
7	Water	359	109.5	63.1	54.8
8	HFIP	469	108.8	65.3	--

[a] Calculated from activation parameters in ref. 11.

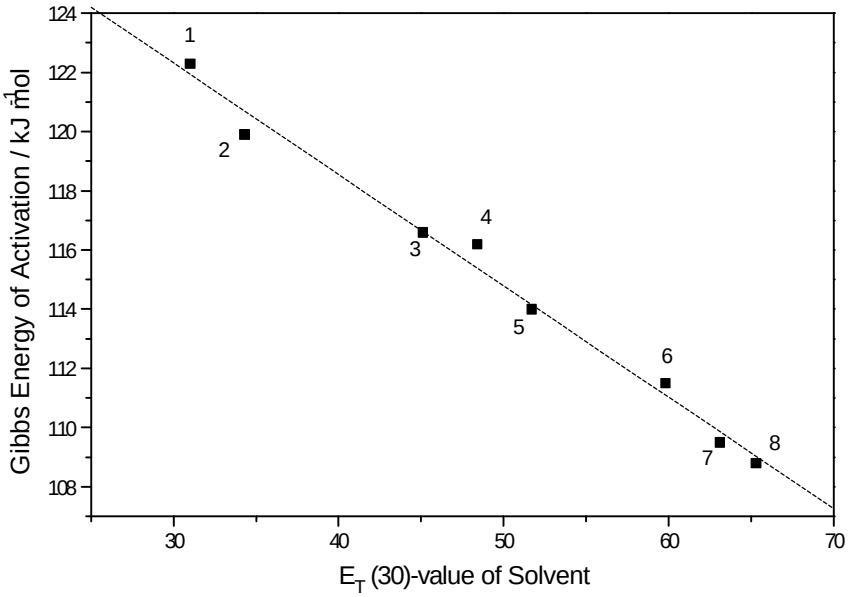


Figure 4.1 *Gibbs energy of activation for the RDA reaction of* ***4.3a*** *vs. the $E_T(30)$-value of the solvents. Numbers correspond to entries in Table 4.1.*

and underlines the notion that also these properties of water contribute to the promotion of all types of DA reactions. The promotion of the RDA reaction by water is related to the effect of this solvent on the Claisen rearrangement, which is also a unimolecular pericylic reaction.

As argued previously, hydrogen bonding of water presumably activates BDA reactions in a similar fashion as RDA reactions. Naturally, the efficiency depends heavily on the sensitivity of the reacting system to accept such hydrogen bonds. At this stage we will compare the RDA reaction of **4.3a**, the BDA reaction of **4.4b** with **4.5** and the IMDA reaction of **4.1**. Because of the kinship of the reacting systems (all systems have two strongly activating substituents next to the dienophilic part), it is reasonable to assume that the former reaction quantitatively reflects similar hydrogen-bond contributions to the bimolecular and intramolecular counterparts.

In Table 4.2 the Gibbs energies of activation for the three DA reactions are compared. The BDA reaction with dienophile **4.4a** is too slow to study and therefore we use the DA reaction of **4.4b** with **4.5** as a model reaction. This hardly affects the interpretation of our results. The RDA and BDA reaction possess almost the same AC and consequently stabilisation of the AC by water is the same for both reactions. Therefore, 12.8 kJ mol^{-1}of the 21.1 kJ mol^{-1} reduction of the $\Delta^{\neq}G^{\theta}$ of the BDA reaction, going from hexane to water, can be assigned to a similar hydrogen-bond stabilisation of the AC. This would leave hydrophobic interactions to contribute the remaining 8.3 kJ mol^{-1} to the fast cycloaddition in water. In Chapter 3 we have proposed that hydrophobic interactions induce a 6.1 kJ mol^{-1} reduction of the $\Delta^{\neq}G^{\theta}$ for 'hydrogen-bond free' DA reactions, but we also pointed out that this quantity is

Table 4.2 *Gibbs Energies of Activation for the RDA Reaction of* ***4.3a*** *(at 40.0 °C), the BDA Reaction of* ***4.4b*** *with* ***4.5*** *(at 25.0 °C) and the IMDA Reaction[5] of* ***4.1*** *(at 40.0 °C) in Organic Solvents and in Water.*

Solvent	$\Delta^{\neq}G^{\theta}_{RDA}$ / kJ mol^{-1} (at 40.0 °C)	$\Delta^{\neq}G^{\theta}_{BDA}$ / kJ mol^{-1} (at 25.0 °C)	$\Delta^{\neq}G^{\theta}_{IMDA}$ / kJ mol^{-1} (at 25.0 °C)[5]
Hexane	122.3	90.5	94.6
Propanol	116.2	83.2	93.2
TFE	111.5	77.9	87.6
Water	109.5	69.4	82.0

probably rather low because of the limited hydrophobicity of the reactants. The reduction of 8.3 kJ mol^{-1} for the $\Delta^{\neq}G^{\theta}$ of the BDA reaction represents the effect of hydrophobic interactions when quite hydrophobic reactants are involved. Taking into account the fact that we have tried to assess the contribution of hydrophobic interactions using two rather different BDA reactions, the two estimates are in reasonable agreement.

Interestingly, the reduction of the $\Delta^{\neq}G^{\theta}$ for the IMDA reaction is of the same magnitude as that for the RDA reaction. Evidently, the carboxylic and amide groups permit water to hydrogen bond efficiently to the IMDA-probe and in this way water activates the dienophilic part of the molecule in a manner similar to the way it activates antracedione **4.3a**. However, **4.1** is not as susceptible to hydrogen bonding as **4.3a**, as a consequence of the inductive effect of the hydroxyl and amine functionalities adjacent to the carbonyl groups. Hence, there is a more moderate rate effect in TFE. Like the BDA reaction, hydrogen bonding of water to the reacting system dominates the acceleration of the IMDA reaction in water.

4.3.2 The Influence of Organic Cosolvents on the Homo Retro Diels-Alder Reaction in Water

Organic cosolvents cause a small additional acceleration of BDA reactions in water[2,5]. The aqueous 'hydrogen-bond free' cycloaddition of acridizinium bromide with cyclopentadiene is also additionally promoted by cosolvents and this suggests that the origin is hydrophobic in nature (see Chapter 3). A study of the cosolvent effect on the RDA reaction will determine if cosolvents also enhance hydrogen bonding of water to the reactants.

Figure 4.2 and Table 4.3 illustrate the cosolvent effect on the RDA reaction of **4.3a**. Most organic cosolvents decrease the first-order rate constant. Opposite to their influence on the BDA reaction, the hydrophobic cosolvents (higher alcohols and 1-cyclohexyl-2-pyrrolidinone (NCHP)) markedly decelerate the cycloreversion, the impact of NCHP being particularly dramatic. The decelerating effect of the alcohols parallels their hydrophobicity. Also acetonitrile induces a substantial rate inhibition, whereas the effect of formamide (which shares some characteristic solvent properties

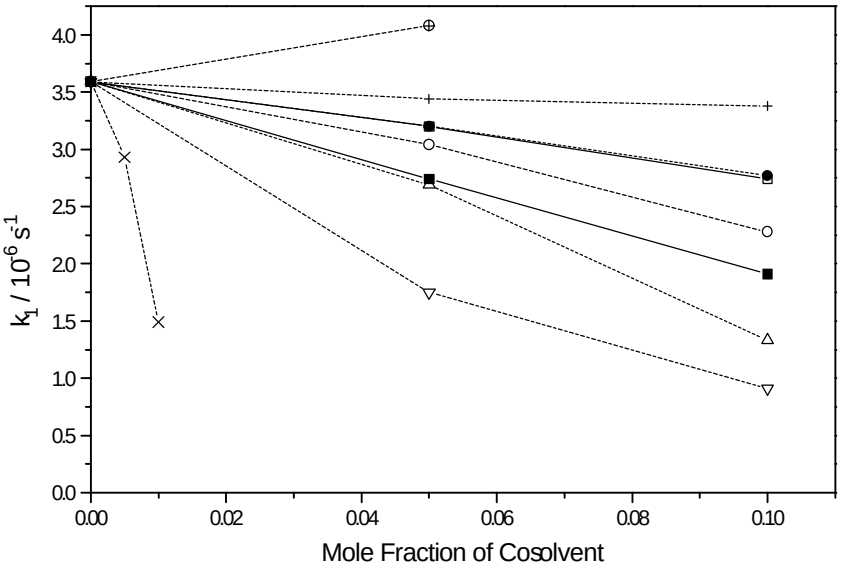


Figure 4.2 *First-order rate constants of the RDA reaction of* ***4.3a*** *vs. mole fraction of organic cosolvents. Cosolvents : MeOH (ÿ), EtOH (*O*), 1-PrOH (*∆*), t-BuOH (*∇*), formamide (●), acetonitrile (*þ*), 1-cyclohexyl-2-pyrrolidinone (×), urea (+), glucose*⊕*.*

with water) is quite modest. Remarkable is the observation that even high concentrations of urea do not interfere with the hydrogen-bond donating capacity of water. Even 10 mol % of urea hardly affects the rate of the RDA reaction in water. The presence of urea remains unnoticed by substrate **4.3a**, because of its good fit into water[28]. Addition of 5 mol % of glucose slightly accelerates the RDA reaction; it is the only added solute that enhances hydrogen bonding to substrate **4.3a**.

The RDA reaction is hardly affected by electrolytes. In KCl-solution (0.5 M) and NaCl-solution (0.5 M) the rate constant for the cycloreversion is $3.36 \cdot 10^{-6}$ and $3.42 \cdot 10^{-6}$ M^{-1} s^{-1}, respectively. The difference of these rates with that in pure water is barely outside experimental error, but nevertheless it indicates that the hydrogen-bond donating capacity of water is slightly reduced. This feature will be of importance in discussing salt effects on bimolecular DA reactions (Chapter 5).

Figure 4.3 illustrates the relationship between the kinetic data of the RDA reaction and the $E_T(30)$-parameter in a number of mixed aqueous solutions. Even for highly aqueous solutions the correlation is satisfactory. In general, solvent parameters of mixed media should be looked at with suspicion, because preferential solvation certainly plays a role in these media and the solvation of a solvatochromic indicator may not be representative for a property of another solute. However, in this case the solvatochromic behaviour of the $E_T(30)$ probe and the reaction rates of **4.3a** are dominated by the same factors.

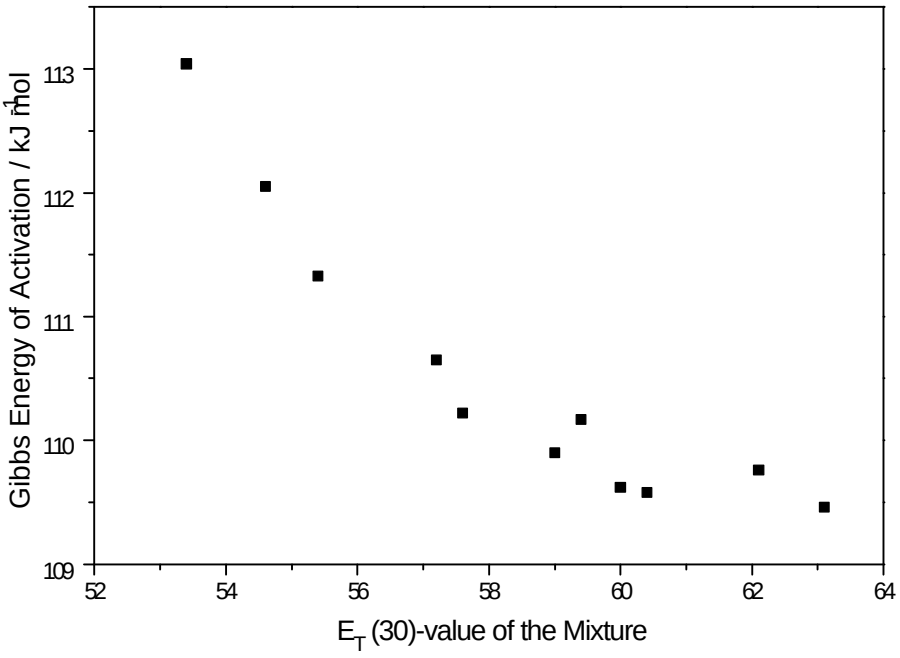


Figure 4.3 *Gibbs energy of activation for the RDA reaction of* ***4.3a*** *vs. the* E_T*(30)-value of the binary aqueous mixtures.*

Assuming that the water-induced accelerations of bimolecular DA reactions are caused by both a hydrogen-bond effect and enforced hydrophobic interactions, we can now discuss the effects that cosolvents exert on bimolecular DA reactions (Table 4.3). The kinetic data for the RDA reaction show

Table 4.3 *Cosolvent Effect on the (Relative*[a]*) First-order Rate Constant of the RDA Reaction of* ***4.3a*** *at 40.0 °C and the (Relative*[a]*) Second-order Rate Constant of the BDA Reaction of* ***4.4b*** *with* ***4.5*** *in Mixed Aqueous Solutions*[b]*.*

Solvent	k_1^{RDA} / 10^{-6} s^{-1}	k^{rel} (RDA)	k_2^{DA} / M^{-1} s^{-1}	k^{rel} (DA)
Water	3.59	1	4.48	1
WM95	3.20	0.89	4.29	0.96
WM90	2.74	0.76	3.80	0.85
WE95	3.04	0.85	4.73	1.06
WE90	2.28	0.64	3.89	0.87
WP95	2.69	0.75	5.14	1.15
WP90	1.33	0.37	1.52	0.34
WB95	1.75	0.49	4.39	0.98
WB90	0.91	0.25	0.90	0.20
WU95	3.44	0.96	3.82	0.85
WU90	3.38	0.94	3.46	0.77
WG95	4.08	1.14	7.40	1.65

[a] See text. [b] WM, WE, WP, WB, WU, WG : aqueous mixtures of methanol, ethanol, 1-propanol, *t*-butanol, urea and glucose, respectively. WM95 indicates a water-MeOH solution containing 95 mol % of water.

that the hydrogen-bond activation of water is decreased upon addition of alcohols to water. Following our rationalisation described in the previous chapters, we conclude that small amounts of alcohol enhance hydrophobic interactions. As a result the BDA reaction proceeds faster.

Addition of urea to water hardly affects the RDA and bimolecular DA reaction, therefore we conclude that urea does not alter the hydrogen-bond capacity of water (as the RDA-results show). The effect of urea on the RDA reaction parallels its influence on the hydrolysis of activated amides[29]. Urea has always enjoyed a special position in the field of 'hydrophobic interactions', because it appears to decrease hydrophobic interactions; for example, urea effectively denaturates proteins[30], increases the critical micelle concentration (CMC) of surfactants[31], enhances the solubility of hydrocarbons in water[32] and disturbs host-guest interactions in water[33]. Originally, these observations were seen as evidence for the ability of urea to act as a water-structure breaker[34], but currently it is thought that urea exerts its influence by specifically interacting with the (*e.g.* micellar or protein) interfaces[35].

The exact effect of urea depends strongly on the nature of the substrate[32,36]. For example, urea promotes the self-association of 1-propanol in water, as indicated by Kirkwood-Buff integrals[37] and NMR-studies[38] . This result indicates that urea enhances hydrophobic interactions. Curiously, the enhanced self-association is confirmed by other experimental studies, but these also show that this association does not occur in the case of *t*-butanol[39]. Combining the results for the RDA and BDA reaction, we conclude that in this case urea slightly diminishes both the hydrogen-bond donating capacity of water (presumably by competing for these bonds) and hydrophobic interactions.

Finally, the glucose-induced acceleration of bimolecular DA reactions seems to be partly caused by enhanced hydrogen bonding of water to the electron-withdrawing substituents of the dienophile, although enhanced hydrophobic interactions again seem to be the dominant cause of the acceleration of the bimolecular DA reaction. The sugar-induced additional rate enhancement of DA reactions in water appears to be general and has been attributed to increased hydrophobic interactions[40]. This may appear strange at first sight, but extensive studies have indeed confirmed that the hydroxyl moieties of carbohydrates often fit into the water structure and hence only the 'bare' hydrophobic methine groups affect chemical processes in solution[41].

4.3.3 The Influence of Surfactants on the Homo Retro Diels-Alder Reaction in Water

In the previous chapters the influence of micelles on the aqueous DA reaction was discussed and the existence of reactant-rich domains was proposed. In Chapter 2 and 3 it was suggested that accumulation of reactants in these domains is accompanied by a reduction of the hydrogen-bond activation. The latter hypothesis is unambiguously confirmed by the kinetic data of the RDA in these solutions.

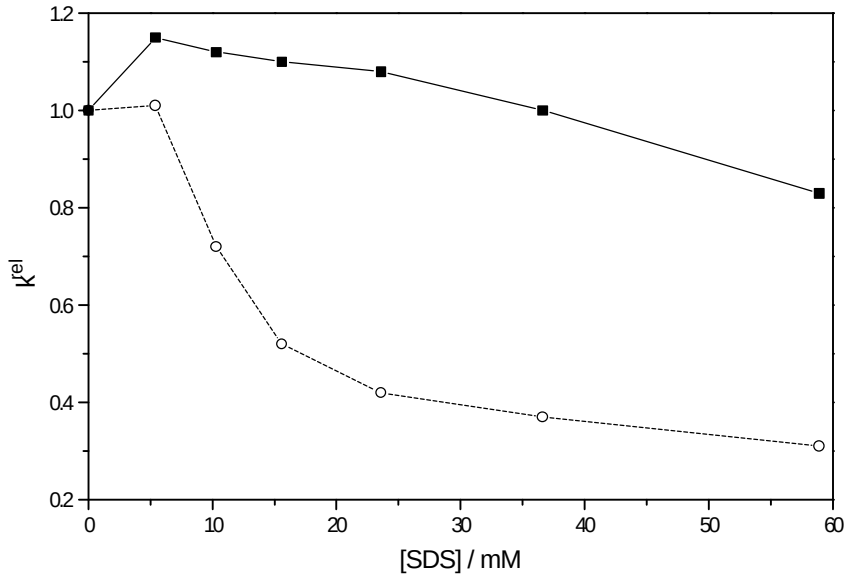


Figure 4.4 *Relative rate constants of the RDA reaction (O) and the BDA reaction (þ) in SDS solutions (see text).*

The influence of SDS micelles on both the RDA reaction of **4.3a** and BDA reaction of **4.4b** with **4.5** was investigated (Figure 4.4). The RDA reaction is clearly decelerated above the critical micelle concentration (CMC) of SDS, although the effect is not dramatic. In fact, at [SDS]= 60 mM the reaction still proceeds markedly faster than in propanol. Keeping in mind the notion that the k_1 directly reflects hydrogen-bond activation by the solvent, this observation shows that water can still interact efficiently with **4.3a**, even when all probe molecules are bound to the micelle.

An interesting parallelism is the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate (6-NBIC), a substrate that has been frequently used as a model compound in studies of enzyme and micelle catalysis[42]. The reaction is slow in water and is generally favoured by aprotic, polar solvents. Solvent effects on the decarboxylation have been fiercely debated, but the rate enhancement in aprotic solvents is now (mainly) ascribed to reduced hydrogen bonding of the solvent on going from the initial state to the transition state[43]. Thus, the strong interaction of water with 6-NBIC severely hinders reaction of this compound. Addition of surfactants to water leads to micellar catalysis above the (kinetic) CMC and in line with the previous explanation this catalysis is attributed to reduced hydrogen bonding at the binding site of the micelle. The effect of micelles on the RDA reaction and the decarboxylation of 6-NBIC are in agreement.

Contrary to the RDA reaction, the BDA reaction is modestly accelerated by a micellar solution (Figure 4.4). Note that even at [SDS]= 5.4 mM (below the CMC) the rate constant is higher than in pure water, possibly due to the formation of mixed SDS-CP aggregates. However, at higher

concentrations of SDS the rate of the BDA reaction is slightly reduced. These observations are in accord with the results of Chapter 2 and 3 and previous reports on DA reactions in micellar media[44,45].

Comparison of the RDA reaction and the BDA reaction and recollection of the results of Chapter 2 and 3 provide a clear picture of the remarkable observation that micelles hardly affect the rate constant of the latter reaction. The kinetic results for the RDA reaction confirm our hypothesis that the activation of the reactants by hydrogen bonding to water is reduced. But apparently the micelles exert a compensating influence, which is the creation of hydrophobic domains in which the concentration of reactants is higher. Kinetic studies on the DA reaction of acridizinium bromide and cyclopentadiene confirmed the existence of such domains in micellar media (Chapter 3). When the concentration of SDS is increased without changing the concentration of **4.5**, these domains become less concentrated in reactant and this leads to the small rate decrease.

So far, we have managed to obtain a rough qualitative picture of DA reactions in micellar media. The details of the micellar rate effects are, however, highly sensitive to small changes in the experimental set-up and detailed experimental work in the future should provide us with a more quantitative description.

4.3.4 Activation Parameters

Isobaric activation parameters of the RDA reaction of **4.3a** present further clues on the origin of the water-induced promotion. Figure 4.5 shows these parameters for the reaction in water-propanol mixtures. The water-induced acceleration is completely caused by a decrease of the $\Delta^{\neq}H^{\theta}$, consistent with enhanced hydrogen bonding in the hydration shell or bonding of water to **4.3a**. Addition of 1-propanol leads to enthalpy-entropy compensatory behavior. When 5 mol % of 1-propanol is added to water the modest increase of the $\Delta^{\neq}G^{\theta}$ for the RDA reaction is the result of an unfavorable $\Delta^{\neq}S^{\theta}$, which is largely compensated by a more favorable $\Delta^{\neq}H^{\theta}$. On increasing the concentration of propanol the $\Delta^{\neq}S^{\theta}$ drops back to zero and the reaction is again completely enthalpy-controlled.

This intriguing compensation effect is often characteristic for chemical processes in aqueous media. The rearrangement of hydrogen bonds of water molecules in the hydration shell can account for this phenomenon and simultaneously explains the accompanying large change of the heat capacity of activation[46]. Again, the small size of the water molecule is considered to play a pivotal role[47]. During the activation process of the RDA reaction the bonds of **4.3a** become polarised and this necessarily causes a change in the hydration of the substrate. This rearrangement is sensitive to the presence of organic cosolvents and is primarily manifested as enthalpy and entropy changes.

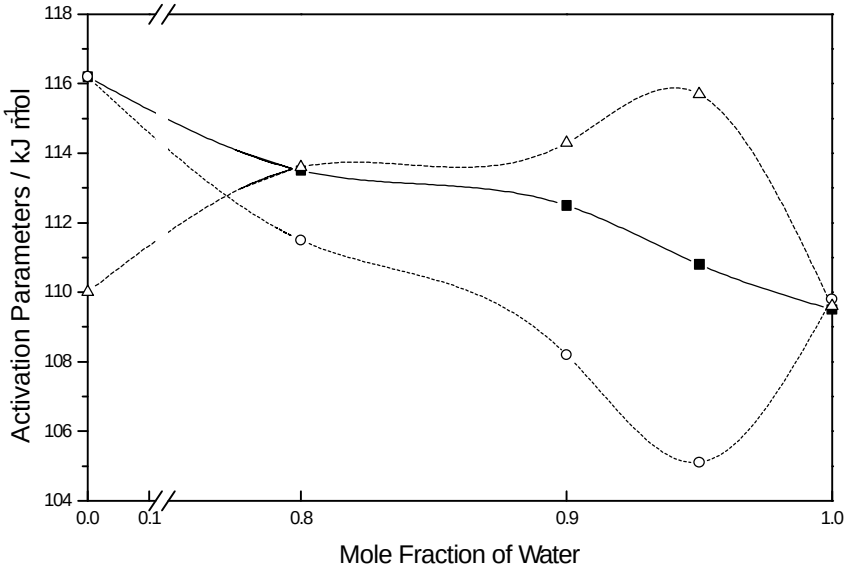


Figure 4.5 *Activation parameters for the RDA reaction of* ***4.3a*** *in water/1-PrOH-mixtures vs. mole fraction of water:* $\Delta G^{\neq}$ (þ), $\Delta H^{\neq}$ (O), $-T.\Delta S^{\neq}$ (Δ). *The* $T.\Delta S^{\neq}$*-plot has been displaced upwards by 110 kJ mol*$^{-1}$ *for clarity.*

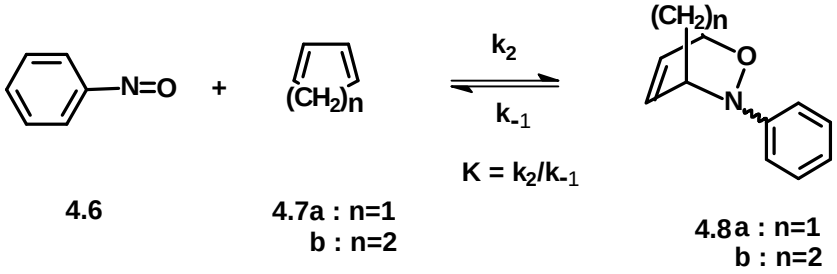
Activation parameters separate the rate enhancements of DA reactions in water into enthalpic and entropic contributions. As mentioned in Chapter 1, reports on activation parameters of BDA reactions are confusing and at times contradictory[2a,40,45]. These parameters are highly dependent on the reactants and the interpretation depends on the reference solvent. The water-induced acceleration can be due to either a more favourable enthalpy or entropy of activation, or mostly, a combination. Activation parameters for the BDA of **4.4b** with **4.5** in pure water reveal nearly equal contributions of the $\Delta^{\neq}H^{\theta}$ and $T.\Delta^{\neq}S^{\theta}$ terms to the rate enhancement in water (relative to 1-propanol)[2a,5]. The reported reduction of the $\Delta^{\neq}H^{\theta}$ for this particular BDA reaction has the same magnitude as the reduction for the RDA reaction; this points to identical hydrogen-bond stabilisation of the AC. Curiously, a more favourable entropy of activation is responsible for the water-induced reduction of $\Delta^{\neq}G^{\theta}$ by 10 kJ mol^{-1} when a substituent (methoxy, hydroxy) is introduced in the 5-position of **4.4b** [2a,5]. This pattern could well be related to the fact that substituents at this position hinder hydrogen bonding of water to the carbonyl group of the naphthoquinone. The activation parameters for the cycloaddition of 5-hydroxy-1,4-naphthoquinone to **4.5** in water/1-propanol mixtures show the same compensating effect over the whole concentration range, albeit far more dramatically than those for the RDA reaction.

4.4 Hetero Retro Diels-Alder Reaction : Results and Discussion

Nitroso compounds react thermally with various dienes to yield dihydro oxazines[48]. Usually mild reaction conditions are sufficient. Activation parameters and substituent effects are typical for DA reactions[49]. For the addition of (substituted) nitrosobenzene (**4.6**) to 1,3-cyclohexadiene (**4.7b**) (Scheme 4.3) a Hammett ρ-value of +2.57 has been established and this points at a rather large change in polarity of the reacting system, on going from the reactants to the AC[50]. However, the concerted nature of this reaction was confirmed by high pressure experiments[51]. Although the adduct of the reaction of **4.6** with **4.7b** is stable at higher temperatures, the product is unstable at room temperature when cyclopentadiene is used as diene, due to the ring strain, which leads to the hetero retro DA (HRDA) reaction of the adduct[52]. However, crystallisation at low temperatures permits isolation of **4.8a**. The equilibrium of this system and the modest solvent effect of the equilibrium constant have been reported previously[53].

Using a concentration of adduct of 0.25 mM, perfect first-order kinetics for the cycloreversion are observed in organic solvents, as the BDA reaction does not interfere at these low concentrations. However, the irreproducibility of the experiments in water leads to the conclusion that in that medium the BDA does compete. Consequently an equilibrium between the dienophile, diene and adduct is established. Further proof came from ^{1}H NMR experiments which also showed the presence of both reactants and cycloadduct, hours after UV/VIS-spectroscopy indicated the end of the reaction. ^{1}H NMR-spectroscopy also shows that the equilibrium constants decrease at higher temperatures.

Desimoni studied the kinetics of the intermolecular DA reactions with p-bromonitrosobenzene in organic solvents and concluded that the cohesive energy density of the solvent is the principle solvent property in determining reaction rates[54]. Previously the efficiency of the DA reaction of **4.6** and **4.7b** in water has been reported[55]. Cyclodextrins catalyse this reaction in water and increase the rate constant by a factor of 15. Acylnitro compounds are unstable in water, but intramolecular DA reactions are possible in aqueous media and lead to the synthesis of alkaloids with enhanced diastereoselectivity[56].



Scheme 4.3

4.4.1 Hetero Retro Diels-Alder Reaction in Organic Solvents and in Water

The solvent sensitivity of the equilibrium constant (K) of the HRDA reaction (Scheme 4.3) is demonstrated by the data in Table 4.4. In this case K is defined as [**4.8a**] / [**4.6**].[**4.7a**]. Even in organic solvents the variation of K is rather large. Our results are in poor agreement with earlier investigations which indicated the absence of any significant solvent influence on the equilibrium[53], but this is probably due to the use of larger concentrations of reactants, which makes the properties of the reaction media more alike.

The change in magnitude of K is comparable to those which are known for DA reactions : in hexane K is the lowest and in TFE it is 93.6 times larger. Attempts to determine the equilibrium constant of the hetero DA reaction in the super-protic solvent HFIP failed due to an unidentified side reaction. Since **4.6** and **4.7** are stable in this solvent the adduct must be susceptible to the side reaction. The K is by far the largest in water, even larger than in TFE, which is as protic as water.

An equilibrium constant is the ratio of the rate constant of the forward and the reverse process ($K = k_2/k_{-1}$)[57]. This implies that the exceptional high K of the hetero cycloreversion is the result of a fast forward or slow reverse reaction (or a combination of these two factors). The simultaneous occurrence of the cycloreversion prevents determination of the second-order rate constants of the cycloaddition of **4.6** with **4.7a**. Therefore the addition of **4.6** to 1,3-cyclohexadiene (**4.7b**) was studied as a model

Table 4.4 *Equilibrium Constants for the HRDA of* ***4.8a****, Second-order Rate Constants for the Cycloaddition of* ***4.6*** *with* ***4.7b*** *and the Apparent First-order Rate Constant*[a] *for the Cycloreversion of* ***4.8a*** *in Organic Solvents and in Water at 25.0 °C.*

Solvent	K / M^{-1}	k_2 / 10^{-2} M^{-1} s^{-1}	k_{-1}^{app} / 10^{-4} s^{-1}
Hexane	6.6	[b]	--
Toluene	12.5	0.96	7.68
Chloroform	24.0	1.18	4.92
Ethanol	35.3	1.10	3.12
1-Propanol	36.1	1.25	3.46
Methanol	43.1	1.10	2.55
DMSO	59.1	2.51	4.25
Formamide	219	6.83	3.12
TFE	618	3.74	0.61
HFIP	[c]	5.27	--
Water	5775	42.5	0.74

[a] The ratio (k_2/K) is defined as the apparent first-order rate constant for the cycloreversion (see text).
[b] The addition of **4.6** to **4.7a** exhibited deviating kinetics, which prevented determination of the rate constant.
[c] No equilibrium was established due to an unknown side reaction. See text.

reaction. These rate constants are also compiled in Table 4.4, together with the calculated 'apparent' k_{-1} of the HRDA reaction of **4.8a**, which was obtained using the equation $K = k_2 / k_{-1}$.

Comparing the rate constants in water and in organic solvents, it turns out that both reactions contribute to the high K in water. The HRDA reaction is decelerated in water and the BDA reaction accelerated, the latter effect being dominant. The acceleration of the BDA reaction is in line with all known aqueous DA reactions and agrees with previous data for the system under study[55].

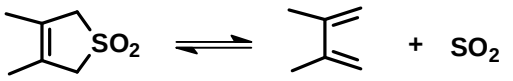
The Gibbs energy of activation of DA reactions can be dramatically reduced in fluorinated alcohols[2], but in the present study the effect is rather modest. This may be attributed to the poor ability of **4.6** to act as hydrogen-bond acceptor[58]. Formamide is the best organic solvent for the cycloaddition, and this suggests that the cohesive energy density (CED) of the solvent plays an important role in this hetero DA reaction, in accord with earlier reports[54]. Obviously, the high rate constant of the bimolecular reaction in water significantly contributes to the high K.

The HRDA reaction responds inversely to a change of solvent. It is retarded in water, and the decomposition proceeds most efficiently in an apolar solvent. In fact, this approach may overestimate contributions of enforced hydrophobic interactions to the bimolecular addition of **4.6** to **4.7a**, because **4.7b** is more hydrophobic than **4.7a** (the aqueous acceleration of the addition of **4.6** to **4.7a** is probably less). Consequently, the 'apparent' first-order rate constants of the cycloreversion could underestimate the retardation of the cycloreversion in water.

This slow HRDA reaction in water may be attributed to the smaller water-accessible surface area of the adduct, which is about 62 % of the surface area of the reactants[59]. But the reaction rate is determined by the difference in Gibbs energy between the reactants and the transition state and the latter will surely resemble the adduct and consequently will have a similar water-accessible surface area.

Instead, we attribute the slow HRDA reaction in water to stabilisation of **4.8a** through efficient hydrogen bonding by water. The IR spectrum of phenol in tetrachloromethane in the presence of **4.8b** reveals two ν_{OH}-shifts (229 and 422 cm^{-1})[60], which confirms that the adduct is a better hydrogen-bond acceptor than **4.6** (110 cm^{-1})[58]. The two peaks arise from bonding to both the nitrogen (229 cm^{-1}) and oxygen atom (422 cm^{-1}) of **4.8b**. The IR-results are in agreement with the fact that isoxazolidines are strong bases with pK_a's around 4-5[61], whereas **4.6** has a pK_a of around 0[62].

The observation that water has an opposite effect on the RDA reaction of **4.3a** and **4.8a**, whereas both rate effects are attributed to hydrogen bonding of water, seems contradictory. However, the dominant factor is the water-induced stabilisation of the AC *relative* to that of the reactant. In the case of the DA reaction of CP and MVK water can interact with the carbonyl moiety of the starting compound, but this interaction is more efficient in the polarised AC[63]. So, in effect the AC is more basic than the reactants and this is an additional incentive for reaction. The same mechanistic pattern is valid for substrate **4.3a**.



4.9 **4.10** **4.11**

Scheme 4.4

For the cycloreversion of **4.8a** the opposite is true. In protic solvents, including water, the AC becomes a less efficient hydrogen bond accepting substrate *relative* to the reactant during the activation process. The polarisation of the bonds that occurs during the activation process has an unfavourable effect on the basicity of both the nitrogen and oxygen atom. Mechanistic studies show that in the AC the nitrogen atom bears a partial positive charge[49], so during the activation process this atom completely looses its basic character. Apparently the enhanced overall polarity of the AC, which is expected on the basis of the large Hammett ρ-value, cannot compensate for this and consequently the interaction between substrate and solvent is decreased. As a result the cycloreversion is retarded in water.

A comparison with Lewis-acid catalysis clarifies this point. A large number of DA reactions can be promoted by the interaction with metal cations. But in Chapter 2 it was shown that the DA reaction of 2,3-dihydrofuran with (substituted) tetrazines is inhibited by Cu^{2+}-ions. Thus an efficient coordination between substrate and medium can also prevent reaction.

An interesting analogy was recently reported by Faita, who studied the solvent effect on a cheletropic reaction (Scheme 4.4)[64]. Cheletropic reactions are concerted $2\pi + 4\pi$ pericyclic reactions in which the new σ-bonds are attached to a single atom of the 2π-system[65]. The bimolecular addition proceeds faster in polar solvents, whereas the reverse reaction is retarded in these solvents. As for the HRDA reaction, an equilibrium constant can be determined, which is shifted by polar solvents to the adduct. Unfortunately only two protic solvents are included in the extensive list of solvents. On the basis of a rather poor correlation with the $E_T(30)$-parameter, Faita points at solvent polarity as the dominating property. Using the Kirkwood-Laidler-Eyring equation and PM3 calculations, he estimates that the polarities of the substrates follow the order **4.9** > AC > **4.10 + 4.11**. The adduct has a larger dipole moment than the AC, therefore the cycloreversion is retarded. The reactants have a smaller dipole moment than the AC, which accelerates the bimolecular process.

An identical mechanism is unlikely for the HRDA reaction. The large Hammett ρ-value for the cycloaddition of nitrosobenzene to various dienes indicates that the AC of these reactions is quite polar[50] and it seems unlikely that adduct **4.8a** is even more polar. For the HRDA reaction the basicity appears important and our results can be explained on the basis of the following order of basicities **4.8a** > AC > **4.6** and **4.7a**.

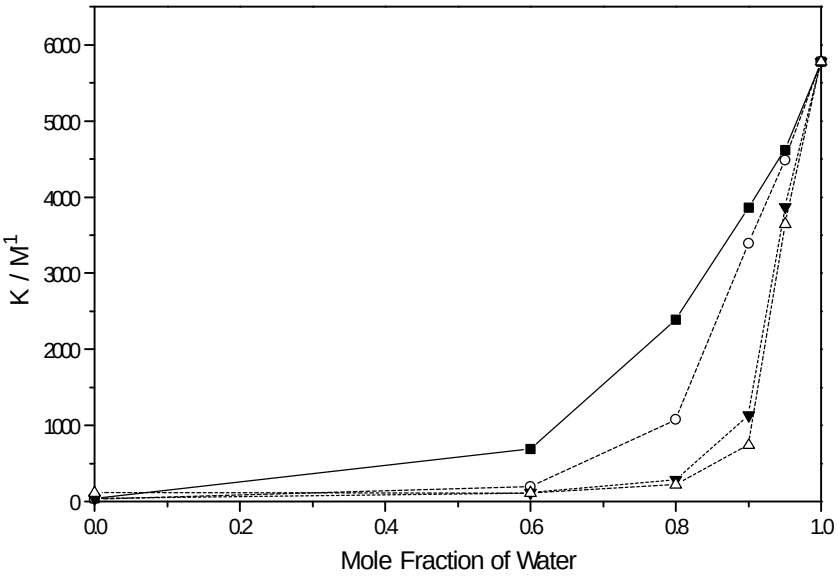


Figure 4.6 *Equilibrium constants for the HRDA reaction of* ***4.8a*** *in water-alcohol mixtures versus the mole fraction of water at 25.0 °C. Cosolvents : MeOH (■), EtOH (O), 1-PrOH (▼), t-BuOH (Δ).*

4.4.2 The Influence of Organic Cosolvents on the Hetero Retro Diels-Alder Reaction in Water

Addition of alcohols to water lowers K similarly to their effect on rate constants of bimolecular DA reactions (Figure 4.6). Hydrophobic alcohols induce a reduction of K at low mole fractions. A noteworthy difference with bimolecular DA reactions is the absence of maxima in K at a characteristic mole fraction of alcohol ($X_{ProH} \approx 0.05$, $X_{BuOH} \approx 0.025$). In previous chapters several examples are given of the additional accelerations which are observed at these mole fractions of hydrophobic cosolvents. These cosolvents do not induce a similar increase in K for the HRDA reaction confirming that hydrophobic interactions are not the dominant factor controlling the equilibrium constant.

The Gibbs energy of the equilibrium and the Gibbs energies of activation for the bimolecular process and the cycloreversion in water/1-propanol mixtures are compared in Figure 4.7. In these media essentially the same factors are operative as in the pure solvents : higher concentrations of water induce a rate enhancement of the bimolecular process and a retardation of the HRDA reaction. Overall this pattern results in the high K in pure water. Note that addition of a small amount of propanol to water is only favourable for the bimolecular process. The Gibbs energy for these processes changes most significantly with changes in solvent composition in the highly aqueous media.

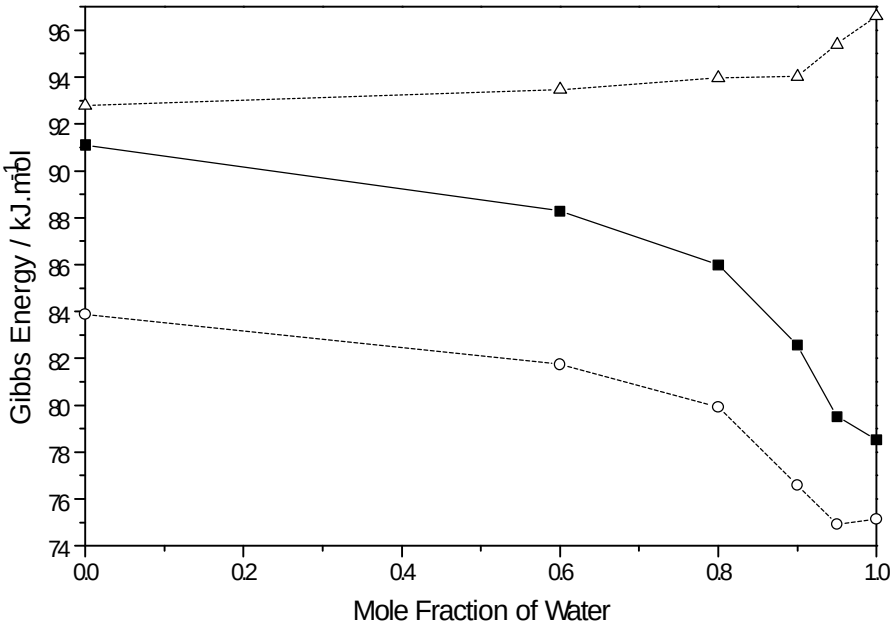


Figure 4.7 *Gibbs energy for the equilibrium of HRDA reaction of* ***4.8a*** *(■)(for clarity this has been displaced upwards by 100 kJ mol^{-1}), and the Gibbs energies of activation for the addition of* ***4.6*** *to* ***4.7b*** *(O) and the cycloreversion of* ***4.8a*** *(Δ) in water/1-PrOH solutions versus the mole fraction of water at 25.0 °C.*

4.4.3 The Influence of Surfactants on the Hetero Retro Diels-Alder Reaction in Water

Micellar solutions solubilise reactants having low solubilities in water. Rate constants of bimolecular DA reactions are roughly of the same order in these media as in water. The specific hydrogen-bond activation of the reactants by water is reduced in micellar solutions, which is unfavourable in terms of reaction rate. But for bimolecular reactions this is largely compensated by the increased local concentration of reactants in the micelle, which promotes the reaction. In SDS-solutions the formation of the adduct is promoted and separation of the contributions to this shift in K shows that in these media both the forward addition and the cycloreversion are promoted (Figure 4.8). The effect of the bimolecular process is dominant and results in an increase of K.

The rate enhancement for the bimolecular cycloaddition is impressive and much larger than previously reported accelerations of neutral DA reactions (10-20 %). This rate enhancement may be explained by taking into account the results in Table 4.4 which show that for this particular bimolecular hetero DA reaction hydrogen-bond interactions contribute less to the rate enhancements in water, as indicated by the modest reaction rates in the fluorinated alcohols. Consequently, the locally increased concentrations of reactants play a dominant role in micellar solutions, leading to the higher observed rate constants.

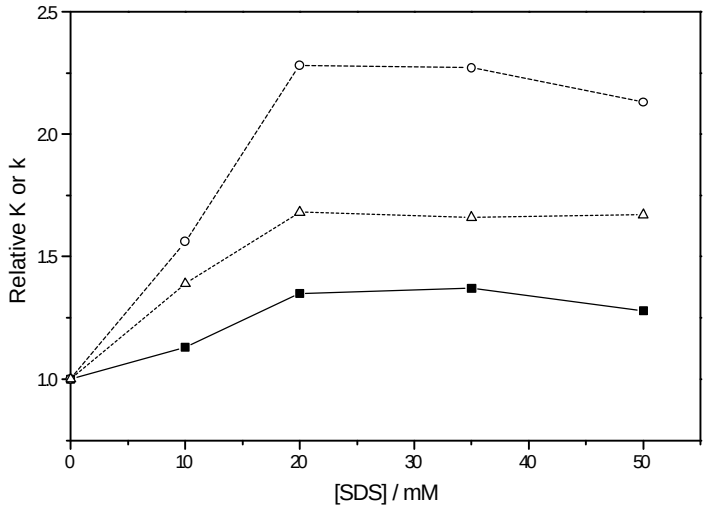


Figure 4.8 *Relative equilibrium constants for the HRDA reaction of* ***4.8a*** *(■), relative second-order rate constant for the DA reaction of* ***4.6*** *and* ***4.7b*** *(*O*) and the relative 'apparent' first-order rate constant for the HRDA reaction of* ***4,8a*** *(*Δ*) versus the concentration of SDS at 25.0 °C.*

The interaction of **4.8a** with micelles leads to a decrease in hydrogen bonding of water to the adduct, thus facilitating decomposition. Again, we draw attention to the analogy with the influence of micelles on the decarboxylation of 6-NBIC[42].

The reproducibility of kinetic data becomes rather poor when concentrations of SDS are just above the critical micelle concentration (CMC) of SDS. This pattern could be due to a sensitivity of the rate constants to the exact composition of the reaction medium, especially the ratio of reactants to surfactant. Clearly, the properties of the micelles are susceptible to small variations of this ratio.

4.4.4 Thermodynamic Parameters

Thermodynamic parameters have been determined for the equilibrium constant and they are in agreement with the model described in previous chapters. These parameters refer to the Gibbs energy of *reaction* and do not give information on the pathway from reactants to an AC. The parameters compare the stability of the reactants and the product. In both 1-PrOH and water the enthalpy term supports formation of the adduct, whereas entropic contributions favour the reactants (Table 4.5). The changes of K (on going from 1-PrOH to water) are largely due to the more negative enthalpic contribution and are only modestly supported by the change in the entropy terms. These results support the notion that water binds more strongly to **4.8a** than to **4.6** and **4.7a** and that hydrophobic effects are of moderate importantance.

Table 4.5 *Thermodynamic Parameters for the HRDA of* ***4.8a*** *in 1-Propanol and Water at 25.0 °C.*

Solvent	ΔG^{θ} / kJ mol^{-1}	ΔH^{θ} / kJ mol^{-1}	$T.\Delta S^{\theta}$ / kJ mol^{-1}
1-PrOH	-8.8	-43.5	-34.7
Water	-21.5	-53.5	-32.0

4.5 Conclusions

In this chapter it has been shown that the retro DA reaction can be both promoted and inhibited by water. The aqueous rate effect depends strongly on the chemical properties of the reactants. The RDA reaction of **4.3a** is accelerated in aqueous solutions, because water can stabilise the AC (relative to the reactant), leading to a considerable reduction of $\Delta^{\neq}G^{\theta}$. Also bimolecular DA reactions are promoted through the same mechanism and possibly to the same extent. The RDA reaction of **4.8a** proceeds more slowly in aqueous media. In this case water stabilises the initial state relative to the AC, because **4.8a** has two basic centres.

4.6 Summarising All Diels-Alder Results

Currently a wealth of kinetic information on DA reactions in aqueous solutions is available. This thesis has added a number of meaningful reactions to the collection. The reactions were selected on the basis of their distinct features, which provided water with different handles to affect the course of the reaction. At this stage some general conclusions can be reached

DA Reactions in Water

Nearly all DA reactions are accelerated in water, the sole exception being the hetero retro DA reaction. In general the polarised AC of DA reactions is efficiently stabilised by water and appears to be less hydrophobic than the reactants. This phenomenon is largely determined by the susceptibility of the AC to hydrogen-bond stabilisation and this is related to the polarisibility of the AC. If the reactant (initial state) interacts too strongly with water, the pericyclic reaction is retarded in water. Therefore the extent of the kinetic effects in water depends significantly on hydrogen-bond accepting properties of the reacting system.

DA Reactions in Aqueous Mixtures

Addition of most cosolvents hampers hydrogen-bonding of water to the AC and for most DA reactions this is unfavourable. But for bimolecular DA reactions this feature may be compensated by a hydrophobic effect, possibly the formation of hydrophobic domains. When the cosolvent is rather hydrophobic, the latter effect is dominant and leads to a further rate enhancement, but usually not more than 10-15 %.

DA Reactions in Micellar Solutions

Addition of surfactants to an aqueous reaction medium creates reactant-rich (usually cyclopentadiene) domains at the micellar surfaces. When reactants are present in such a domain, they are usually deactivated, because the interaction with water is disturbed. But the concentration of the reactants is also increased in these domains, which promotes the cycloaddition. These two effects are counteractive and usually balance each other. If, however, the reacting partners are forced into these domains micellar catalysis becomes feasible.

In Chapter 6 we examine the validity of these conclusions for 1,3-dipolar cycloadditions.

4.7 Experimental Section

Homo Retro Diels-Alder Reaction

Synthesis and Product Analysis

1,4,4a,9a-Tetrahydro-4a-methyl-(1α,4α,4aα,9aα)-1,4-methaneanthracene-9,10-dione **4.3a** was synthesized according to a literature procedure[11] and was crystallized several times from cyclohexane, m.p. 97 °C (lit.[11] 96 °C). On a synthetic scale the RDA reaction was carried out as follows : 50 mg of **4.3a** was dissolved in 5 ml of acetonitrile and this solution was added dropwise to 200 ml of water. The slightly turbid solution was stirred overnight at 70-80 °C. After cooling, the yellow solution was extracted several times with chloroform, dried with sodium sulfate and finally the solvent was removed. ^{1}H NMR-analysis only revealed the presence of **4.4a.**

Kinetic Experiments

Rate constants were determined for solutions in thermostatted cuvets, using a Perkin-Elmer Lambda 2, 5 or 12 UV/VIS-spectrometer. Water was distilled twice in an all-quartz distillation unit. Solvents were of the best available quality or were distilled before use. The homo RDA reaction was monitored at 340 nm and the first-order rate constant was determined using the initial rate method[57]. This method is less accurate than conventional pseudo-first-order kinetics, but enables determination of a large number of rate constants of slow reactions. The extinction coefficient is required of both **4.3a** and **4.4a**. The extinction coefficients of the compounds in the highly aqueous solutions did not significantly differ from

those in pure water. A few microliters of a stock-solution of **4.3a** dissolved in propanol were added to the cuvets, initial concentrations of **4.3a** were 0.2-20 mM.. The first-order rate constants are the average of at least five independent experiments and were reproducible to within 4 %. Activation parameters were calculated from rate constants at four different temperatures in the range 30-49 °C.

The DA reaction (**4.4a** + **4.5** → **4.3a**) does not affect the kinetics of the RDA reaction : addition of a large excess of acrylonitrile (to scavenge **4.5**) does not change the observed rate constants. The rate constants of the bimolecular DA reaction of **4.4b** with **4.5** were measured as described previously[2a].

Determination of E_T(30)-values

The E_T(30)-values of the aqueous mixtures were measured on a Perkin-Elmer Lambda 2 UV/VIS-spectrometer, following a literature procedure[66].

Hetero Retro Diels-Alder Reaction

Synthesis and Product Analysis

Adduct **4.8a** was prepared by mixing 300 mg of nitrosobenzene (**4.6**) and a large excess of freshly distilled cyclopentadiene (**4.7a**) in 25 ml of anhydrous ether. After the characteristic blue colour of nitrosobenzene had vanished, the ether and excess of cyclopentadiene were removed *in vacuo*. The remaining solid was dissolved in pentane and this solution was slowly cooled down to -80 °C. This yielded a white solid, m.p. = 33 °C (lit.[52]: 32-34 °C). **4.8b** was prepared in a similar fashion.

Kinetic Experiments

Equilibrium constants of the hetero RDA reaction were determined several times by injecting a known amount of a stock solution of **4.8a** in acetonitrile to cuvets, which contained a known amount of solvent. The reaction was followed in a thermostated cell (25.0 ± 0.1 °C) of a UV/VIS spectrometer (Perkin Elmer Lambda 2, 5 or 12). The formation of nitrosobenzene was monitored at 308 nm. After establishing that **4.8a** has no absorbance at this wavelength, the extinction coefficients of nitrosobenzene in all solvents were measured, using three different concentrations (reproducibility 2%). In most experiments the adduct was prepared *in situ* by mixing known amounts of nitrosobenzene, cyclopentadiene and acetonitrile (typically 10 mg of nitrosobenzene, 40 mg of cyclopentadiene and 1 ml of acetonitrile), and this mixture was used as stock solution. This procedure produced identical results and yielded equilibrium constants with a reproducibility of 4 %. Water was distilled twice and the organic solvents were either P.A. quality or distilled before use. Thermodynamic parameters were estimated by measuring equilibrium constants at 5 temperatures in the range 15-36 °C.

Similarly, the second-order rate constants for the addition of nitrosobenzene to (distilled) 1,3-cyclohexadiene were determined at 308 nm. An excess of cyclohexadiene ensured pseudo-first-order

conditions. Generally the reproducibility was within 2%, but in SDS solutions around the CMC the reproducibility was within 10 %.

^{1}H NMR-spectroscopy

Solutions of **4.8a** in $CDCl_3$ and in D_2O/CD_3OD ($X_W \approx 0.95$) showed the presence of **4.7a** (δ 3.0 (CH_2), 6.47 and 6.58 (CH)), **4.8** (δ 7.58-7.94) and the adduct **4.8a** (δ 1.80 (d, 1H), 2.18 (d, 1H), 5.00 (s, 1H), 5.18 (s, 1H), 5.96 (m, 1H), 6.38 (m, 1H), 6.88-7.24 (m, 5H)).

IR-spectroscopy

The hydrogen-bond accepting capacity of **4.8b** was determined using a Perkin-Elmer 841 IR-spectrometer following a literature procedure[58].

Acknowledgement

Evert van Rietschoten and Frans Wessels are thanked for carrying out the initial experiments on the homo RDA reaction. Rob Zijlstra is gratefully acknowledged for calculating the solvent-accessible surface area of **4.6**, **4.7a** and **4.8a**.

4.8 References

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